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Mandibuloacral Dysplasia in An Iranian Girl

Mandibuloacral dysplasia (MAD) is a rare autosomal recessive syndrome. Less than 25 families have been reported, most of which are Italian. Here, we describe a new patient of Iranian origin, born to consanguineous parents.

Keywords: laminopathy, lipodystrophy, mandibuloacral dysplasia

Introduction

Mandibuloacral dysplasia [MIM 248370(Mendelian Inheritance in Man)] is a rare autosomal recessive disorder characterized by mandibular and clavicular hypoplasia, acro-osteolysis, delayed closure of cranial suturs and joint contractures.[1,2] Moreover they may develop metabolic derangement as insulin resistance, hypertriglyceridemia, and lipodystrophy.[3, 4] It is shown that MAD is a genetically and phenotypically heterogeneous disorder.[1] As of now, it has been reported in less than 25 families, most of which are Italian.[5,6] Here we present a new patient from the north east of Iran with typical clinical and radiologic features of this syndrome.

Case Report

The patient was a 7-year-old girl, who was referred to our center for evaluation of her short stature. She was the third child of a consanguineous marriage. She was born at full term by cesarean section. The perinatal period was uneventful. Her two elder brothers had died in infancy, probably of cardiomyopathy. She has been otherwise healthy until 2 years of age, at which she developed growth retardation, progressive stiffness of all joints, swelling of phalanges, and mottled hyperpigmentation of the acral regions.

On physical examination, she had a weight of 18 kg, height of 110 cm, and head circumference of 46.5 cm. Her neurological status was appropriate for age. There was generalized loss of subcutaneous fat. Skin was hyperpigmented with some hypopigmentation over the extensor surfaces. The sagittal suture and both fontanelles were wide open. Her scalp hair was slate gray and scant. Teeth were poorly implanted and overcrowded. On the lateral view, beaked nose and micrognathia were prominent (Figure 1). Both clavicles were hypoplastic, and shoulders could be drawn together. Active and passive ranges of motion of all joints, especially distal ones, were diminished. Distal phalanges were shortened resulting in the expansion of fingertips (Figure 2). Laboratory studies revealed hypertriglyceridemia, and a normal serum insulin level (Table1).

Convential radiography showed open cranial sutures, as well as osteolysis of the distal phalanges, and mandibular and clavicular hypoplasia (Figure 3). The mastoid airspaces were poorly aerated. As the patient had no history of mastoiditis,

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Table 1. Clinical and laboratory features of the presented patient with MAD

Growth retardation
Micrognathia
Bird-like facies
Clavicular hypoplasia
Acro-osteolysis
Wide cranial sutures
Skin atrophy
Mottled cutaneous pigmentation
Joint contracture
Generalized lipodystrophy
Dental abnormalities
Alopecia
Plasma insulin level : 10um/ml (normal range: 7-24)

this could have been a developmental feature of MAD syndrome.

Discussion

Here we presented a girl with clinical features compatible with MAD. Parental consanguinity and positive family history made the autosomal recessive pattern of inheritance very likely. MAD is a syndrome that principally affects connective tissues. The clinical picture is protean and each patient may have several features of the syndrome. These patients acquire a progeric complexion, which should be differentiated from other syndromes of premature aging.[1,7]

In addition to phenotypic changes, these patients may have some metabolic abnormalities. These include hypertriglyceridemia, insulin resistance, and even overt diabetes mellitus.[3,8] Our patient had a normal blood level of insulin and a normal glucose tolerance test; however, insulin resistance may develop over time. A component of the syndrome is lipodystrophy. This is commonly associated with insulin resistance. Two patterns of lipodystrophy are seen in these patients. Some patients have partial lipodystrophy (type A) with excess subcutaneous fat in the neck and truncal regions and loss of fat in extremities.[3,8] Mutation in LMNA gene has been reported in these type patients.[9] LMNA encodes lamins A and C, which are components of the nuclear envelop. [10] Another group of MAD patients (MADB) has generalized or type B lipodistrophy.[8] Mutations in LMNA have not been found in MADB patients that have been studied.[1] In a woman with MADB, compound heterozygotic mutations were found in the zinc metalloproteinase gene.[11] Zinc metaloproteinase is involved in post-translational modification of prelamin A to lamin A.[11]

MADA and MADB, both belong to laminopathies. Laminopathies are a group of inherited diseases with heterogenous features, arising from mutations in coding genes for A type lamins and lamin A associated proteins.[7] Why these different disorders arise from mutations in the same gene yet remains to be determined.

Phenotypic changes of MADA begin at 4–5 years of life, while MADB has been reported to begin earlier.[11] According to the pattern of lipodystrophy and age of onset of the clinical features, it seems that our patient suffers from MAD with type B lipodystrophy; however, we could not perform mutation analysis for this patient. Presence of cardiomyopathy in her sib-

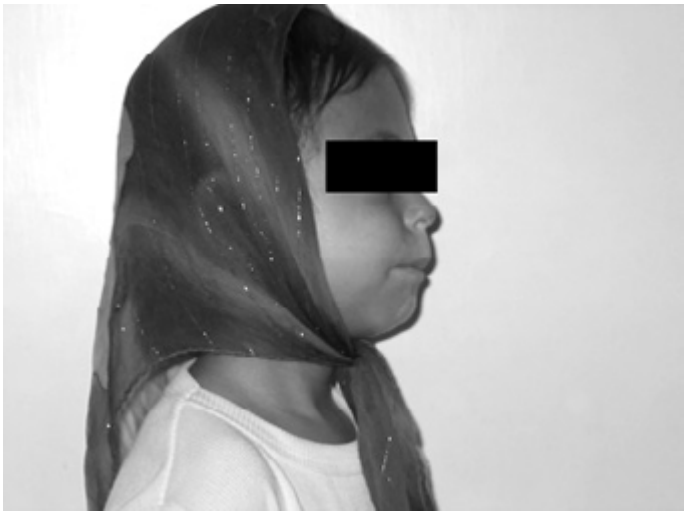

Fig 1. Micrognathia and beaked nose producing a bird-like face.

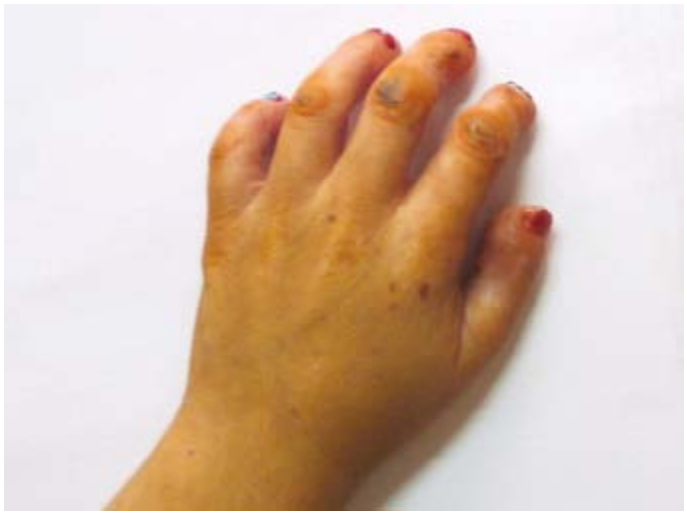

Fig 2. Shortening of distal phalanges, and blunting of fingertips.

lings is also compatible with laminopathy.[7]

MAD has clinical and radiologic features in common with some other syndromes. Progressive skeletal changes are salient in this syndrome. Mandibular and clavicular hypoplasia, delayed closure of cranial sutures and acro-osteolysis are radiologically visible. Cleidocranial dysplasia [CD (MIM 119600)]; a radiologically similar entity should be excluded in cases with aforementioned radiologic manifestations. CD is characterized with drooping shoulders, open fontanelles, prominent forehead, and dental abnormalities. Acral changes and progeroid features are not seen in this syndrome. CD has a benign course with no metabolic derangement. MAD also should be considered in the differential diagnosis of juvenile scleroderma in the presence of atypical features such as negative serological studies, absence of Raynaud's phenomenon, sparse hair and micrognathia.[12]

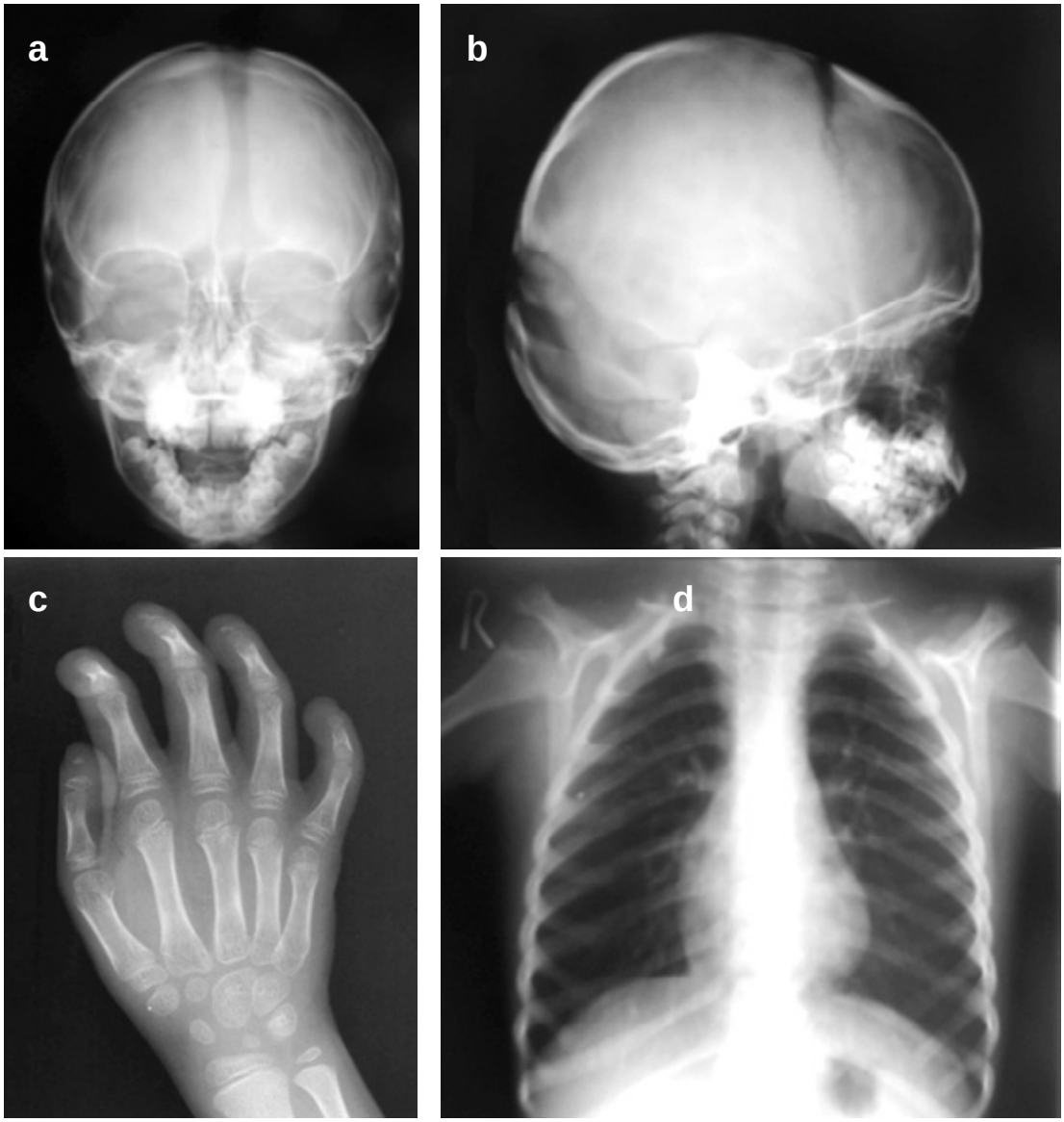

Fig 3. Radiography shows open cranial sutures (a), mandibular hypoplasia (b), clavicular hypoplasia (c), and osteolysis of distal phalanges (d).

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